OMIM Home Search Comments

\*167415 PAIRED BOX GENE 8; PAX8

Alternative titles; symbols

PAIRED DOMAIN GENE 8
PAX8/PPARG FUSION GENE, INCLUDED

Krollet al appear to be first to rame PAXB-PPARIZ

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## **Database Links**

MEDLINE Protein DNA HGMD LocusLink Gene Map GDB Nomenclature

Gene Map Locus: 2q12-q14

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#### **TEXT**

#### **DESCRIPTION**

Pax genes encode a family of transcription factors that are essentially required for the formation of several tissues from all germ layers in the mammalian embryo. Specifically, in organogenesis, they are involved in triggering early events of cell differentiation. In the thyroid gland, PAX8 is essential for the formation of thyroxine-producing follicular cells, which are of endodermal origin (Mansouri et al., 1999).

#### **CLONING**

<u>Plachov et al. (1990)</u> identified in the mouse a paired box gene, designated Pax8, expressed in the developing excretory system and in the thyroid gland.



#### **GENE FUNCTION**

Pasca di Magliano et al. (2000) demonstrated that PAX8 is sufficient to activate expression of endogenous genes encoding thyroglobulin (TG; 188450), thyroperoxidase (TPO; 274500), and sodium/iodide symporter (SLC5A5; 601843), all thyroid-specific genes. The cell system they used provided direct evidence for the ability of PAX8 to activate transcription of thyroid-specific genes at their chromosomal locus and strongly suggested a fundamental role of this transcription factor in the maintenance of functional differentiation in thyroid cells. Moreover, they showed that PAX8 and thyroid transcription factor-1 (600635) cooperate in the activation of the thyroglobulin promoter.  $_{\mathbb{Q}}$ 

#### **MAPPING**

Walther et al. (1991) mapped the Pax8 gene to proximal mouse chromosome 2 in a region showing extensive conserved linkage homology to human 9q. Contrary to expectation, however, the human homolog of Pax8 did not map to 9q. Using a mouse cDNA probe for Pax8 in the analysis of somatic cell hybrids, Pilz et al. (1993) mapped the PAX8 gene to human chromosome 2. Other data suggested that the mouse gene lies close to the boundary of the 9q/mouse chromosome 2 homology group and that it represents a new conserved segment between human chromosome 2 and mouse chromosome 2, lying proximal to that between human chromosome 9 and mouse chromosome 2. By analysis of somatic cell hybrids and by fluorescence in situ hybridization, Stapleton et al. (1993) assigned the PAX8 gene to 2q12-q14. 'Danforth's short tail' (Sd) is a semidominant mutation of the mouse with effects on the skeleton and urogenital system. Although the Sd locus is on mouse chromosome 2, Koseki et al. (1993) demonstrated recombinants between the Sd locus and the Pax8 locus. 

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#### **MOLECULAR GENETICS**

In 80 to 85% of cases of permanent congenital hypothyroidism, the disorder is associated with, and presumably is a consequence of, thyroid dysgenesis (218700). In these cases, the thyroid gland can be absent (agenesis, 35 to 40%), ectopically located (30 to 45%), and/or severely reduced in size (hypoplasia, 5%). Familial cases of thyroid dysplasia are rare, even though ectopic or absent thyroid has been occasionally observed in sibs. Mutations in the gene encoding the receptor for the thyroid-stimulating hormone (TSHR; 603372) have been identified in only 2 cases of thyroid dysgenesis with hypoplasia. Macchia et al. (1998) reported mutations in the coding region of PAX8 in 2 sporadic cases and 1 familial case of thyroid dysplasia. All 3 point mutations are located in the paired (Prd) domain of PAX8 and resulted in severe reduction in the DNA-binding activity of this transcription factor. These genetic alterations implicated PAX8 in the pathogenesis of thyroid dysgenesis and in normal thyroid development. In each of these cases the mutation was present in heterozygous state. 

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The Pax proteins are transcriptional regulators that recognize specific DNA sequences via a conserved element, namely, the paired domain. The low level of organized secondary structure, in the free state, is a general feature of Prd domains; however, these proteins undergo a dramatic gain in alpha-helical content upon interaction with DNA ('induced fit'). <u>Tell et al. (1999)</u> investigated the molecular defects caused by the leu62-to-arg mutation of PAX8 (167415.0004). Leu62 is conserved





among Prd domains, and contributes to the packing together of helices 1 and 3. <u>Tell et al. (1999)</u> showed that the gain in alpha-helical content upon interaction of the DNA is greatly reduced in the mutant protein as compared to the wildtype protein. Thus, the molecular defect of the leu62-to-arg mutant causes a reduced capability for induced fit upon DNA interaction.

#### **CYTOGENETICS**

#### PAX8/PPARG1 Fusion Gene

Kroll et al. (2000) reported that t(2;3)(q13;p25), a translocation identified in a subset of human thyroid follicular carcinomas, results in fusion of the DNA-binding domains of PAX8 to domains A to F of the peroxisome proliferator-activated receptor gamma-1 (PPARG1; 601487). PAX8/PPARG1 mRNA and protein were detected in 5 of 8 thyroid follicular carcinomas but not in 20 follicular adenomas, 10 papillary carcinomas, or 10 multinodular hyperplasias. PAX8/PPARG1 inhibited thiazolidinedione-induced transactivation by PPARG1 in a dominant-negative manner. The experiments demonstrated an oncogenic role for PPARG and suggested that PAX8/PPARG1 may be useful in the diagnosis and treatment of thyroid carcinoma.

#### ANIMAL MODEL

The thyroid gland develops from 2 distinct embryonic lineages: follicular cells, which produce thyroxine and are of endodermal origin, and parafollicular C-cells, which produce calcitonin and are of neural crest origin. Mice lacking thyroid transcription factor-1 (600635) lack both cell types and thus are unable to develop a thyroid gland. By analysis of Pax8 knockout mice (Pax8 -/-), Mansouri et al. (1998) demonstrated that Pax8 is required for the formation of the follicular cells in the thyroid. They presented evidence that Pax8 is necessary for providing cues for the differentiation of component endoderm primordia into thyroxine-producing follicular cells. ©

## **ALLELIC VARIANTS**

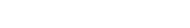
### (selected examples)

#### .0001 PAX8 POLYMORPHISM [PAX8, PHE329LEU]

Considering PAX8 as a possible candidate gene for nephronophthisis (NPH1; 256100), which maps to the same region of 2q, Torban et al. (1997) screened the PAX8 gene using SSCP analysis for mutations associated with NPH1. No disease-associated mutations were found, but the first PAX8 polymorphism, phe329 to leu (F329L), was found in 1 of 15 patients and 2 of 20 controls. This polymorphic variant involves a conserved amino acid change in the C-terminal portion of the PAX8 protein. It lies outside the known paired-box domain; thus, a drastic effect on protein activity could not be expected. Nonetheless, a subtle effect could not be excluded.

### .0002 THYROID DYSGENESIS [PAX8, ARG108TER]

In an infant with thyroid ectopy and reduced gland size (218700), Macchia et al. (1998) identified heterozygosity for a C-to-T substitution in the first position of codon 108 of the PAX8 gene, changing CGA (arg) to TGA (stop) in exon 3. The nonsense mutation was predicted to result in the



synthesis of truncated protein containing only the first 100 amino acids of the paired domain. The mutation was found in neither of the parents nor in the affected brother, indicating that it was a de novo mutation.

#### .0003 THYROID DYSGENESIS [PAX8, ARG31HIS]

In an infant with thyroid hypoplasia (218700), thyroid-stimulating hormone (see 188540) levels almost 100-fold above normal, and T4 levels well below normal (measured 10 days after birth), Macchia et al. (1998) found heterozygosity for a G-to-A transition in exon 2 of the PAX8 gene, which changed codon 31 from CGC (arg) to CAC (his). All other family members were unaffected and homozygous for the wildtype CGC codon.

## .0004 THYROID DYSGENESIS [PAX8, LEU62ARG]

Following the birth of a child with congenital hypothyroidism, a mother and her son and daughter were found to have hypothyroidism due to thyroid hypoplasia (218700). All affected members of the family were heterozygous for the same T-G transversion, converting codon 62 of the PAX8 gene from CTT (leu) to CGT (arg). Considerable variability in the severity of the clinical manifestations was observed in this family.

#### .0005 THYROID DYSGENESIS [PAX8, CYS57TYR]

<u>Vilain et al. (2001)</u> described a novel mutation in the PAX8 gene causing autosomal dominant transmission of congenital hypothyroidism with thyroid hypoplasia (<u>218700</u>). The mutation consists of a cys57-to-tyr substitution in the paired domain of PAX8. When tested in cotransfection experiments with a thyroid peroxidase promoter construct, the mutant allele was unable to exert its normal transactivation effect on transcription. The authors concluded that, contrary to the situation in knockout mice, haploinsufficiency of PAX8 is a cause of congenital hypothyroidism in humans.

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Victor A. McKusick: 11/5/1992

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# ALLELIC VARIANTS (selected examples)

• 0001: PAX8 POLYMORPHISM

• Mutation: PAX8, PHE329LEU

• 0002 : THYROID DYSGENESIS

• Mutation: PAX8, ARG108TER



• 0003: THYROID DYSGENESIS

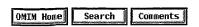
• Mutation: PAX8, ARG31HIS

• <u>0004 : THYROID DYSGENESIS</u>

• Mutation: PAX8, LEU62ARG

• <u>0005 : THYROID DYSGENESIS</u>

• Mutation: PAX8, CYS57TYR



# \*601487 PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-GAMMA; PPARG

Alternative titles; symbols

PPARG1, INCLUDED
PPARG2, INCLUDED
PPARG3, INCLUDED
PAX8/PPARG FUSION GENE, INCLUDED

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## **Database Links**



Gene Map Locus: 3p25

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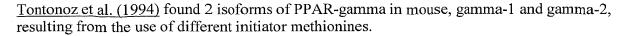
#### **TEXT**

#### DESCRIPTION

The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor subfamily of transcription factors. PPARs form heterodimers with retinoid X receptors (RXRs) and these heterodimers regulate transcription of various genes. There are 3 known subtypes of PPARs, PPAR-alpha (170998), PPAR-delta (600409), and PPAR-gamma. PPAR-gamma is believed to be involved in adipocyte differentiation. 

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#### **CLONING**



Elbrecht et al. (1996) cloned cDNAs of PPAR-gamma-1 and PPAR-gamma-2 from human fat cell cDNA by PCR using primers based on the mouse sequence and on a previously published human cDNA sequence (Greene et al., 1995). They found that the human PPAR-gamma-1 and PPAR-gamma-2 genes have identical sequences except that PPAR-gamma-2 contains an additional 84 nucleotides at its 5-prime end. The sequences obtained by Elbrecht et al. (1996) differed at 3 sites from the previously published human PPAR-gamma-1 sequence of Greene et al. (1995). By Northern blot analysis, Elbrecht et al. (1996) found that human PPAR-gamma is expressed at high levels in adipocytes and at a much lower level in bone marrow, spleen, testis, brain, skeletal muscle, and liver.

<u>Fajas et al. (1997)</u> used competitive RT-PCR to distinguish relative PPARG1 and PPARG2 mRNA levels in tissues. They determined that PPARG2 is much less abundant than PPARG1. The highest levels of PPARG are found in adipose tissue and large intestine, with intermediate levels in kidney, liver, and small intestine, and barely detectable levels in muscle. Western blot analysis showed that PPARG is expressed as a 60-kD protein. EMSA analysis indicated that PPARG2 binds to and transactivates through a peroxisome proliferator response element. Through alternative transcription start sites and alternate splicing, the PPARG mRNAs differ at their 5-prime ends, with PPARG1 being encoded by 8 and PPARG2 by 7 exons. PPARG1 uses exons A1 and A2, whereas PPARG2 uses exon B; both use exons 1 through 6.

Martin et al. (1998) reported that there are 3 PPARG isoforms which differ at their 5-prime ends, each under the control of its own promoter. PPARG1 and PPARG3, however, give rise to the same protein, encoded by exons 1 through 6, because neither the A1 nor the A2 exon are translated.

Fajas et al. (1998) identified the third PPARG isoform, PPARG3, which is transcribed from a novel promoter localized 5-prime of exon A2. The promotor region contains a TATA-like element, a CAAT-like sequence, and a potential E box. PPARG3 mRNA expression was restricted to adipose tissue and to large intestine.

#### GENE FUNCTION

The thiazolidinediones are synthetic compounds that can normalize elevated plasma glucose levels in obese, diabetic rodents and may be efficacious therapeutic agents for the treatment of noninsulin-dependent diabetes mellitus. Lehmann et al. (1995) identified the thiazolidinediones as high affinity ligands for mouse PPAR-gamma receptors. Elbrecht et al. (1996) confirmed that human PPAR-gamma-1 and PPAR-gamma-2 have similar activity and determined that 3 different thiazolidinedione compounds are agonists of PPAR-gamma-1 and PPAR-gamma-2. Elbrecht et al. (1996) speculated that the antidiabetic activity of the thiazolidinediones in humans is mediated through the activation of PPAR-gamma-1 and PPAR-gamma-2. ©

By semiquantitative RT-PCR analysis of freeze-dried muscle samples from 14 male subjects, <u>Lapsys et al. (2000)</u> examined the potential regulation of genes by PPARG in human skeletal muscle. The expression of 3 genes important in lipid metabolism, lipoprotein lipase (see <u>238600</u>),



muscle carnitine palmitoyltransferase-1 (601987), and fatty acid-binding protein (e.g., 134650), correlated significantly with PPARG expression in the same samples. The authors concluded that these findings support the hypothesis that PPARG activators such as the antidiabetic thiazolidinediones may regulate fatty acid metabolism in skeletal muscle as well as in adipose tissue. 

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Mueller et al. (1998) showed that PPAR-gamma is expressed at significant levels in human primary and metastatic breast adenocarcinomas. Ligand activation of this receptor in cultured breast cancer cells caused extensive lipid accumulation, changes in breast epithelial gene expression associated with a more differentiated, less malignant state, and a reduction in growth rate and clonogenic capacity of the cells. Inhibition of MAP kinase, a powerful negative regulator of PPAR-gamma, improves the thiazolidinedione ligand sensitivity of nonresponsive cells. These data suggested that the PPAR-gamma transcriptional pathway can induce terminal differentiation of malignant breast epithelial cells.

Tontonoz et al. (1994) identified a novel adipocyte-specific transcription factor, which they termed ARF6, and showed that it is a heterodimeric complex of RXRA and PPARG. (This ARF6 is not to be confused with ADP-ribosylation factor 6 (600464), with is also symbolized ARF6.) Tontonoz et al. (1995) demonstrated that PPAR-gamma-2 regulates adipocyte expression of the phosphoenolpyruvate carboxykinase gene (PCK1, 261680; PCK2, 261650).

Tarrade et al. (2001) examined the expression and role of the PPARG/RXRA heterodimers in human invasive trophoblasts. They reported that in human first-trimester placenta, PPARG and RXRA are highly expressed in cytotrophoblasts at the fetomaternal interface, especially in the extravillous cytotrophoblasts involved in uterus invasion. They also found that both synthetic and natural PPARG agonists inhibit extravillous cytotrophoblast invasion in a concentration-dependent manner and synergize with pan-RXR agonists. They concluded that these data underscore an important function of PPARG/RXRA heterodimers in the modulation of trophoblast invasion.

The formation of foam cells from macrophages in the arterial wall is characterized by dramatic changes in lipid metabolism, including increased expression of scavenger receptors and the uptake of oxidized low density lipoprotein (oxLDL). Tontonoz et al. (1998) demonstrated that the nuclear receptor PPAR-gamma is induced in human monocytes following exposure to oxLDL and is expressed at high levels in the foam cells of atherosclerotic lesions. Ligand activation of the PPAR-gamma:RXR-alpha heterodimer in myelomonocytic cell lines induced changes characteristic of monocytic differentiation and promoted uptake of oxLDL through transcriptional induction of the scavenger receptor CD36. These results revealed a novel signaling pathway controlling differentiation and lipid metabolism in monocytic cells. Tontonoz et al. (1998) suggested that endogenous PPAR-gamma ligands may be important regulators of gene expression during atherogenesis. 

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Nagy et al. (1998) demonstrated that oxLDL activates PPAR-gamma-dependent transcription through a signaling pathway involving scavenger receptor-mediated particle uptake. Moreover, they identified 2 of the major oxidized linoleic acid metabolite components of oxLDL, 9-HODE and 13-HODE, as endogenous activators and ligands of PPAR-gamma. The authors found that the biologic effects of oxLDL are coordinated by 2 sets of receptors, one on the cell surface, which binds and internalizes the particle, and one in the nucleus, which is transcriptionally activated by its component lipids. Nagy et al. (1998) suggested that PPAR-gamma may be a key regulator of foam cell gene expression.



Chawla et al. (2001) provided evidence that in addition to lipid uptake, PPARG regulates a pathway of cholesterol efflux. PPARG induces ABCA1 (600046) expression and cholesterol removal from macrophages through a transcriptional cascade mediated by the nuclear receptor LXRA (NR1H3; 602423). Ligand activation of PPARG leads to primary induction of LXRA and to coupled induction of ABCA1. Transplantation of PPAR null bone marrow into Ldlr -/- mice resulted in a significant increase in atherosclerosis, consistent with the hypothesis that regulation of LXRA and ABCA1 expression is protective in vivo. Chawla et al. (2001) proposed that PPARG coordinates a complex physiologic response to oxLDL that involves particle uptake, processing, and cholesterol removal through ABCA1.

Sewter et al. (2002) examined the relationship between BMI and PPARG isoform expression in freshly isolated human adipocytes. In a group of 17 subjects there was a strong and highly significant inverse correlation (r = -0.68; P less than 0.005) between PPARG1 mRNA expression in adipocytes and BMI, whereas no significant relationship was apparent for PPARG2. Vidal-Puig et al. (1997) had demonstrated that PPARG1 mRNA levels were decreased in adipocytes from morbidly obese subjects. In contrast, there was a significant increase in the expression of PPARG2 mRNA levels between the morbidly obese and lean groups. Sewter et al. (2002) concluded that the strong inverse relationship between BMI and PPARG1 expression in human adipocytes may represent part of an autoregulatory mechanism restraining the expansion of individual adipocytes in states of positive energy balance.

By RNase protection analysis, <u>Ricote et al. (1998)</u> showed that in phorbol ester-stimulated macrophage cell lines, a probe to PPARG1 protected a 218-nucleotide fragment of PPARG1, but only a 174-nucleotide fragment of PPARG3. A PPARG2 probe protected a common 104-nucleotide fragment of both PPARG1 and PPARG3. PPARG2 itself was not expressed in the stimulated macrophages. PPARG1 and PPARG2 promoters are primarily used in adipose tissue. The authors speculated that other inducing factors, such as cytokines MCSF (120420) or GMCSF (138960), or oxidized LDL (see OLR1, 602601), might differentially regulate expression of the 3 isoforms.

Rosen et al. (2002) created an immortalized mouse fibroblast cell line lacking Pparg. They found that both Cebpa (116897) and Pparg were involved in fat cell development; however, Cebpa required Pparg to promote adipogenesis. Rosen et al. (2002) concluded that Pparg is downstream of Cebpa in the adipogenesis pathway.

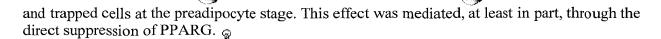
Utilizing engineered zinc finger repressor proteins expressed in an adipogenic mouse cell line, <u>Ren et al. (2002)</u> found evidence that Pparg2, and not Pparg1, is required for adipogenesis.

Using primary human lung bronchial epithelial cells and several human lung epithelial cell lines, <u>Pawliczak et al. (2002)</u> found evidence that CPLA2 (see <u>600522</u>) has a role in the control of PPARG expression.

Lowell (1999) reviewed the role of PPARG in adipogenesis.

Kersten et al. (2000) reviewed the roles of PPARs in health and disease.

Tong et al. (2000) showed that murine GATA2 (137295) and GATA3 (131320) are specifically expressed in white adipocyte precursors and that their downregulation sets the stage for terminal differentiation. Constitutive GATA2 and GATA3 expression suppressed adipocyte differentiation



Mueller et al. (2000) showed that PPAR-gamma is expressed in human prostate adenocarcinomas and cell lines derived from these tumors. Activation of this receptor with specific ligands exerts an inhibitory effect on the growth of prostate cancer (176807) cell lines. They showed that prostate cancer and cell lines do not have intragenic mutations in the PPARG gene, although 40% of the informative tumors have hemizygous deletions of this gene. They conducted a phase II clinical study in patients with advanced prostate cancer using troglitazone (Rezulin), a PPAR-gamma ligand used for the treatment of type II diabetes. Oral treatment was administered to 41 men with histologically confirmed prostate cancer and no symptomatic metastatic disease. An unexpectedly high incidence of prolonged stabilization of prostate-specific antigen (KLK3; 176820) was seen in patients treated with troglitazone. In addition, 1 patient had a dramatic decrease in serum prostate-specific antigen to nearly undetectable levels. The findings suggested that PPAR-gamma may serve as a biologic modifier in human prostate cancer and that its therapeutic potential should be further studied.

Harris and Phipps (2002) showed that prostaglandin D2 (PGD2; see 176803) induced apoptosis in T-cell leukemia and lymphoma cell lines but not in normal peripheral blood T cells. The malignant T cells, but not the normal T cells, expressed mRNA for DPR, the PGD2 receptor (PTGDR; 604687); however, DPR agonists failed to induce apoptosis. RT-PCR and immunocytochemical analysis demonstrated that the malignant T cell lines, but not normal resting T cells, expressed PPARG mRNA as well as cytoplasmic and nuclear PPARG protein. In addition, PPARG agonists, but not PPARA (170998) agonists, mimicked the action of PGD2 and its metabolite, 15-d-PGJ2, in inhibiting the proliferation and viability of the T-cell tumor lines and in inducing apoptosis in these cells. Harris and Phipps (2002) concluded that PPARG ligands, which may include PGD2, provide strong apoptotic signals to transformed but not normal T lymphocytes.

Ge et al. (2002) demonstrated that Trap220 -/- fibroblasts are refractory to PPAR-gamma-2-stimulated adipogenesis, but not to MyoD-stimulated myogenesis, and do not express adipogenesis markers or PPAR-gamma-2 target genes. These defects could be restored by expression of exogenous TRAP220. Further indicative of a direct role for TRAP220 in PPARG2 function via the TRAP complex, TRAP functioned directly as a transcriptional coactivator for PPARG2 in a purified in vitro system and interacted with PPARG2 in a ligand- and TRAP220-dependent manner. Ge et al. (2002) concluded that TRAP220 acts, via the TRAP complex, as a PPARG2-selective coactivator and, accordingly, that it is specific for 1 fibroblast differentiation pathway (adipogenesis) relative to another (myogenesis).

Adrenocorticotrophic hormone (ACTH)-secreting pituitary tumors are associated with high morbidity due to excess glucocorticoid production. Heaney et al. (2002) demonstrated immunoreactive expression of PPAR-gamma exclusively in normal ACTH-secreting human anterior pituitary cells. Furthermore, PPAR-gamma was abundantly expressed in all of 6 human ACTH-secreting pituitary tumors studied. PPAR-gamma activators induced G0/G1 cell cycle arrest and apoptosis and suppressed ACTH secretion in human and murine corticotroph tumor cells. Development of murine corticotroph tumors, generated by subcutaneous injection of ACTH-secreting AtT20 cells, was prevented in 4 of 5 mice treated with the thiazolidinedione compound rosiglitazone, and ACTH and corticosterone secretion was suppressed in all treated mice. Based on these findings, Heaney et al. (2002) suggested that thiazolidinediones may be an effective therapy for Cushing disease (219090). ©





#### **GENE STRUCTURE**

Fajas et al. (1997) determined that the PPARG gene contains 9 exons and spans more than 100 kb.

#### **MAPPING**

By somatic cell hybridization and linkage analysis, <u>Greene et al. (1995)</u> mapped the human PPARG gene to 3p25. <u>Beamer et al. (1997)</u> mapped the gene to 3p25 by fluorescence in situ hybridization.

#### **MOLECULAR GENETICS**

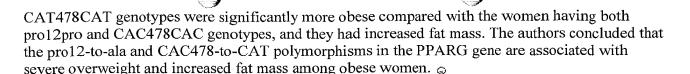
Meirhaeghe et al. (1998) detected a polymorphism corresponding to a silent C-to-T substitution in exon 6 of the PPARG gene (601487.0009).

Since PPARG is a transcription factor that has a key role in adipocyte differentiation, <u>Ristow et al.</u> (1998) investigated whether mutations of the gene encoding this factor predispose people to obesity. They studied 358 unrelated German subjects, including 121 obese subjects, looking for mutations in the PPARG2 gene at or near a site of serine phosphorylation at position 114 that negatively regulates transcriptional activity of the protein. Four of the 121 obese subjects had a missense mutation in the PPARG2 gene that resulted in conversion of proline to glutamine at position 115 (601487.0001), as compared with none of the 237 subjects of normal weight. All the subjects with the mutant allele were markedly obese. Overexpression of the mutant gene in murine fibroblasts led to the production of a protein in which the phosphorylation of serine at position 114 was defective, as well as accelerated differentiation of the cells into adipocytes and greater cellular accumulation of triglyceride than with the wildtype PPAR-gamma-2. These effects were similar to those of an in vitro mutation created directly at the ser114 phosphorylation site. ©

PPARG1 and PPARG2 have ligand-dependent and -independent activation domains. PPARG2 has an additional 28 amino acids at the amino terminus that render its ligand-independent activation domain 5- to 10-fold more effective than that of PPARG1. Insulin stimulates the ligand-independent activation of PPARG1 and PPARG2; however, obesity and nutritional factors influence only the expression of PPARG2 in human adipocytes. Deeb et al. (1998) reported that a relatively common pro12-to-ala substitution in PPARG2 (601487.0002) is associated with lower body mass index and improved insulin sensitivity among middle-aged and elderly Finns. A significant odds ratio (4.35, P = 0.028) for the association of the pro/pro genotype with type 2 diabetes (125853) was observed among Japanese Americans. The PPARG2 ala allele showed decreased binding affinity to the cognate promoter element and reduced ability to transactivate responsive promoters. These findings suggested that the PPARG2 pro12-to-ala polymorphism may contribute to the observed variability in BMI and insulin sensitivity in the general population. 

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<u>Valve et al. (1999)</u> investigated the frequencies of the pro12-to-ala polymorphism in exon B and the silent CAC478-to-CAT polymorphism in exon 6 of the PPARG gene and their effects on body weight, body composition, and energy expenditure in obese Finnish patients. The frequencies of the ala12 allele in exon B and the CAT478 allele in exon 6 were not significantly different between the obese and population-based control subjects (0.14 vs 0.13 and 0.19 vs 0.21, respectively). The polymorphisms were associated with increased BMI, and the 5 women with both ala12ala and



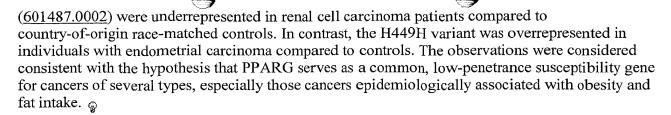
Sarraf et al. (1999) identified 4 somatic mutations (1 nonsense, 1 frameshift, and 2 missense) in the PPARG gene among 55 sporadic colon cancers (114500). Each mutation greatly impaired the function of the PPARG protein. The 472delA mutation (601487.0003) resulted in the deletion of the entire ligand binding domain. Q286P (601487.0004) and K319X (601487.0005) retained a total or partial ligand binding domain but lost the ability to activate transcription through a failure to bind to ligands. R288H (601487.0006) showed a normal response to synthetic ligands but greatly decreased transcription and binding when exposed to natural ligands. These data indicated that colon cancer in humans is associated with loss-of-function mutations in the PPARG gene. ©

Conflicting studies showing that synthetic ligands such as thiazolidinediones can influence the frequency of colonic tumors in mice raised concerns about the role of PPAR-gamma in colon cancer. Girnun et al. (2002) analyzed critically the role of this receptor in mice heterozygous for the Pparg gene with both chemical and genetic models of colon cancer. Heterozygous loss of the gene function caused an increase in beta-catenin levels and a greater incidence of colon cancer when animals were treated with azoxymethane. However, mice with preexisting damage to the Apc gene (175100), a regulator of beta-catenin, developed tumors in a manner insensitive to the status of the Pparg gene. These data showed that PPAR-gamma can suppress beta-catenin levels and colon carcinogenesis but only before damage to the APC/beta-catenin pathway. Thus, PPAR-gamma ligands may be useful as chemopreventive agents in colon cancer.

Barroso et al. (1999) reported 2 different heterozygous mutations in the ligand-binding domain of PPARG in 3 subjects with severe insulin resistance (604367). In the PPAR-gamma crystal structure, the mutations destabilized helix 12, which mediates transactivation. Consistent with this, both receptor mutants were markedly transcriptionally impaired and, moreover, were able to inhibit the action of coexpressed wildtype PPAR-gamma in a dominant-negative manner. In addition to insulin resistance, all 3 subjects developed type 2 diabetes mellitus and hypertension at an unusually early age. Barroso et al. (1999) concluded that their findings represented the first germline loss-of-function mutations in PPAR-gamma and provided compelling genetic evidence that this receptor is important in the control of insulin sensitivity, glucose homeostasis, and blood pressure in man. ©

Kroll et al. (2000) reported that t(2;3)(q13;p25), a translocation identified in a subset of human thyroid follicular carcinomas, results in fusion of the DNA-binding domains of the thyroid transcription factor PAX8 (167415) to domains A to F of PPARG1. PAX8/PPARG1 mRNA and protein were detected in 5 of 8 thyroid follicular carcinomas but not in 20 follicular adenomas, 10 papillary carcinomas, or 10 multinodular hyperplasias. PAX8/PPARG1 inhibited thiazolidinedione-induced transactivation by PPARG1 in a dominant-negative manner. The experiments demonstrated an oncogenic role for PPARG and suggested that PAX8/PPARG1 may be useful in the diagnosis and treatment of thyroid carcinoma.

Because of somatic mutations of PPARG in sporadic colorectal cancers and because of the somatic translocation of PAX8 and PPARG in follicular thyroid carcinoma, as well as the overrepresentation of the H449H variant (601487.0010) in glioblastoma multiforme, Smith et al. (2001) examined a broader range of cancers for germline sequence variation in PPARG. They found that P12A alleles



Savage et al. (2002) described a family they referred to as a 'Europid pedigree' with several members with severe insulin resistance. The grandparents had typical late-onset type 2 diabetes (125853) with no clinical features of severe insulin resistance. Three of their 6 children and 2 of their grandchildren had acanthosis nigricans, a dermatologic marker of extreme insulin resistance. All 5 of these individuals with acanthosis nigricans had markedly elevated fasting plasma insulin levels. By mutational screening, Savage et al. (2002) identified a heterozygous frameshift resulting in a premature stop mutation of the PPARG (601487.0011) gene that was present in the grandfather, all 5 relatives with severe insulin resistance, and 1 other relative with normal insulin levels. Further candidate gene studies revealed a heterozygous frameshift/premature stop mutation in PPP1R3A (600917.0003) that was present in the grandmother, in all 5 individuals with severe insulin resistance, and in 1 other relative. Thus, all 5 family members with severe insulin resistance, and no other family members, were double heterozygotes with respect to frameshift mutations. A note on terminology: the affected individuals were double heterozygotes, not compound heterozygotes. Compound heterozygosity is heterozygosity at the same locus for each of 2 different mutant alleles; double heterozygosity is heterozygosity at each of 2 separate loci. The use of incorrect terms in the original publication was the result of a 'copy-editing error that was implemented after the authors returned corrected proofs.' (Savage et al., 2002).

#### **BIOCHEMICAL FEATURES**

FMOC-L-leucine (F-L-leu) is a chemically distinct PPARG ligand. Rocchi et al. (2001) found that 2 molecules of F-L-leu bind to the ligand-binding domain of a single PPARG molecule, making its mode of receptor interaction distinct from that of other nuclear receptor ligands. F-L-leu induces a particular allosteric configuration of PPARG resulting in differential cofactor recruitment and translating in distinct pharmacologic properties. F-L-leu activates PPARG with a lower potency that rosiglitazone, but with a similar maximal efficacy. The particular PPARG configuration induced by F-L-leu leads to a modified pattern of target gene activation. F-L-leu improves insulin sensitivity in normal, diet-induced glucose-intolerant, and diabetic db/db mice, yet it has a lower adipogenic activity. These biologic effects suggest that F-L-leu is a selective PPARG modulator that activates some (insulin sensitization) but not all (adipogenesis) PPARG-signaling pathways. §

Aljada et al. (2001) examined the possibility that troglitazone may modulate the expression of PPARA and PPARG. Seven obese hyperinsulinemic subjects were administered 400 mg troglitazone daily for 4 weeks. Fasting blood samples were obtained before and during troglitazone therapy at 1, 2, and 4 weeks. Fasting insulin concentrations fell at week 1 and persisted at lower levels until 4 weeks. PPARG expression fell significantly at week 1 and fell further at weeks 2 and 4. In contrast, PPARA expression increased significantly at week 2 and further at week 4. Two products of linoleic acid peroxidation and agonists of PPARG, 9- and 13-hydroxyoctadecanoic acid, decreased during troglitazone therapy. The authors concluded that troglitazone, an agonist for both PPARA and PPARG, has significant but dramatically opposite effects on PPARA and PPARG. They also concluded that these effects may be relevant to its insulin sensitizing and



antiinflammatory effects.

## Crystal Structure

The nuclear receptor PPARG/RXRA heterodimer regulates glucose and lipid homeostasis and is the target for the antidiabetic drugs GI262570 and the thiazolidinediones. <u>Gampe et al. (2000)</u> reported the crystal structures of the PPARG and RXRA ligand-binding domains complexed with the RXRA ligand 9-cis-retinoic acid, the PPARG agonist GI262570, and coactivator peptides. The structures provided a molecular understanding of the ability of RXRs to heterodimerize with many nuclear receptors and of the permissive activation of the PPARG/RXRA heterodimer by 9-cis-retinoic acid.

#### ANIMAL MODEL

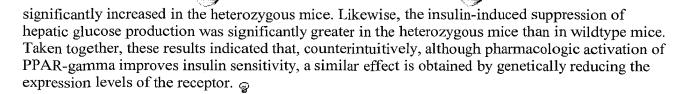
The nuclear hormone receptor PPARG promotes adipogenesis and macrophage differentiation and is a primary pharmacologic target in the treatment of type II diabetes. <u>Barak et al. (1999)</u> showed that PPARG gene knockout in mice resulted in 2 independent lethal phases. Initially, PPARG deficiency interfered with terminal differentiation of the trophoblast and placental vascularization, leading to severe myocardial thinning and death by E10.0. Supplementing PPARG null embryos with wildtype placentas via aggregation with tetraploid embryos corrected the cardiac defect, implicating a previously unrecognized dependence of the developing heart on a functional placenta. A tetraploid-rescued mutant surviving to term exhibited another lethal combination of pathologies, including lipodystrophy and multiple hemorrhages. These findings both confirmed and expanded the current known spectrum of physiologic functions regulated by PPARG. 

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Kubota et al. (1999) generated homozygous PPARG-deficient mouse embryos, which died at 10.5 to 11.5 days postcoitum due to placental dysfunction. Heterozygous PPARG-deficient mice were protected from the development of insulin resistance due to adipocyte hypertrophy under a high-fat diet. These phenotypes were abrogated by PPARG agonist treatment. Heterozygous PPARG-deficient mice showed overexpression and hypersecretion of leptin despite the smaller size of adipocytes and decreased fat mass, which may explain these phenotypes at least in part. This study revealed an unpredicted role for PPARG in high-fat diet-induced obesity due to adipocyte hypertrophy and insulin resistance, which requires both alleles of PPARG.

Rosen et al. (1999) demonstrated that mice chimeric for wildtype and PPARG null cells showed little or no contribution of null cells to adipose tissue, whereas most other organs examined did not require PPARG for proper development. In vitro, the differentiation of embryonic stem cells into fat was shown to be dependent on PPARG gene dosage. These data provided direct evidence that PPARG is essential for the formation of fat. §

The thiazolidinedione (TZD) class of insulin-sensitizing, antidiabetic drugs interacts with PPAR-gamma. Miles et al. (2000) conducted metabolic studies in PPARG gene knockout mice. Because homozygous PPARG-null mice die in development, they studied glucose metabolism in mice heterozygous for the mutation. They identified no statistically significant differences in body weight, basal glucose, insulin, or free fatty acid levels between the wildtype and heterozygous groups. Nor was there a difference in glucose excursion between the groups of mice during oral glucose tolerance tests. However, insulin concentrations of the wildtype group were greater than those of the heterozygous deficient group, and insulin-induced increase in glucose disposal rate was



Using RNase protection and in situ hybridization, <u>Michalik et al. (2001)</u> showed that the alpha, delta, which they called beta, and gamma isotypes of PPAR are expressed in the mouse epidermis during fetal development and that they disappear progressively from the interfollicular epithelium after birth. <u>Michalik et al. (2001)</u> generated Pparg mutant mice and observed early embryonic lethality of Pparg-null mutants, consistent with the findings of <u>Barak et al. (1999)</u> and <u>Kubota et al. (1999)</u>.

Using the Cre-loxP system, Akiyama et al. (2002) generated conditional Pparg-deficient mice lacking exon 2 of the gene, which encodes the DNA-binding region of the protein. The majority of elicited peritoneal macrophages maintained an intact Pparg gene. Induction of Cre recombinase resulted in loss of exon 2 and marked reductions in basal and troglitazone-stimulated expression of the lipoprotein lipase, Cd36 (173510), Lxra, and Abcg1 (603076) genes. In addition, there were reductions in the basal levels of apolipoprotein E (apoE; 107741) mRNA in macrophages and apoE protein and high-density lipoprotein (HDL) in plasma. Basal cholesterol efflux from cholesterol-laden macrophages to HDL was significantly reduced. Troglitazone, but not other thiazolidinedione compounds, inhibited Abca1 expression and cholesterol efflux in both control and Pparg-deficient macrophages. Akiyama et al. (2002) concluded that PPARG plays an important role in the regulation of cholesterol homeostasis by controlling the expression of a network of genes that mediate cholesterol efflux from cells and its transport in plasma.

Using the Cre-loxP system, <u>Cui et al. (2002)</u> targeted disruption of Pparg to several mouse organs and tissues. They found that Pparg was not required for functional development of the mammary gland during pregnancy or for the establishment of B and T cells. Absence of Pparg did not increase the incidence of mammary tumors. However, the loss of Pparg in oocytes and granulosa cells resulted in impaired fertility. Progesterone levels were decreased and implantation rates were reduced. 

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## **ALLELIC VARIANTS**

## (selected examples)

## .0001 OBESITY, SEVERE [PPARG, PRO115GLN]

In 4 German subjects with severe obesity (601665), Ristow et al. (1998) identified a prol 15-to-gln mutation of the PPAR-gamma-2 gene. Significantly, the mutation was in the codon immediately adjacent to a serine-114 phosphorylation site. The prol 15-to-gln mutation occurs in exon 6, which is shared by all 3 forms of PPAR-gamma Wang et al. (1999).

## .0002 DIABETES MELLITUS, TYPE II, RESISTANCE TO [PPARG, PRO12ALA]

Because the product of the PPARG gene is a nuclear receptor that regulates adipocyte differentiation and possibly lipid metabolism and insulin sensitivity, <u>Yen et al. (1997)</u> screened for mutations in the entire coding region of the PPARG gene in 26 diabetic Caucasians with or without





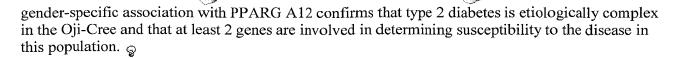
obesity (601665). They found a CCG (pro)-to-GCG (ala) missense mutation at codon 12 (pro12 to ala; P12A). The allele frequency of the mutation varied from 0.12 in Caucasian Americans to 0.10 in Chinese. Beamer et al. (1998) noted that the amino acid position of the P12A mutation is within the domain of PPAR-gamma-2 that enhances ligand-independent activation, that the substitution of alanine for proline is nonconservative, and that this amino acid change might cause a significant alteration in protein structure. To test the hypothesis that individuals with the variant are at increased genetic risk for obesity and/or insulin resistance, they performed association studies in 2 independently recruited cohorts of unrelated, nondiabetic, adult Caucasian subjects. They found that the P12A mutation was associated with higher BMI in the 2 cohorts, suggesting that the mutation may contribute to genetic susceptibility for the multifactorial disorder of obesity. 

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Deeb et al. (1998) studied a polymorphism of the PPARG gene, a C-to-G variant that created an HgaI restriction site and predicted the substitution of alanine for proline at position 12 in the PPARG2-specific exon B. In a group of Finnish men and women with a PPARG2 ala allele frequency of 0.12, they found that this allele was associated with lower fasting insulin levels (P =0.011) and BMI (P = 0.027) and higher insulin sensitivity (P = 0.047). This association was independent of sex. The findings were verified by studies in a group of elderly subjects. They also studied the association of the pro12-to-ala substitution in PPARG2 with type 2 diabetes (125853) in a group of second-generation Japanese-American (Nisei) men and women that included individuals with type 2 diabetes, impaired glucose tolerance, and normal controls. The ala allele was less frequent among subjects with type 2 diabetes (0.022) than among normal controls (0.092). The odds ratio for association of pro/pro with diabetes was significant (4.35, P = 0.028), whereas the frequency of the ala allele among impaired glucose tolerance subjects was intermediate (0.039). Deeb et al. (1998) suggested that the lower transactivation capacity of the ala variant of PPARG2 underlies the association of this allele with lower BMI and higher insulin sensitivity. The ala isoform may lead to less efficient stimulation of PPARG target genes and predispose to lower levels of adipose tissue mass accumulation, which in turn may be responsible for improved insulin sensitivity.

Altshuler et al. (2000) evaluated 16 published genetic associations to type 2 diabetes and related subphenotypes using a family-based design to control for population stratification, and replication samples to increase power. They confirmed only 1 association, that of the common pro12-to-ala polymorphism in PPAR-gamma with type 2 diabetes. By analyzing over 3,000 individuals, they found a modest (1.25-fold) but significant (P = 0.002) increase in diabetes risk associated with the more common proline allele (approximately 85% frequency). Because the risk allele occurs at such high frequency, its modest effect translates into a large population-attributable risk--influencing as much as 25% of type 2 diabetes in the general population.  $\bigcirc$ 

Hegele et al. (2000) found that the G319S (142410.0008) variant was strongly associated with type 2 diabetes among the Oji-Cree of northern Ontario. However, the majority of subjects with diabetes did not have the HNF1A S319 variant, suggesting that there might be other genetic determinants of diabetes susceptibility. In the course of sequencing candidate genes in diabetic subjects who were homozygous for HNF1A G319/G319, they found that some subjects had the PPARG A12 variant. After genotyping PPARG in the entire adult Oji-Cree population, they found that: (1) PPARG A12 was strongly associated with type 2 diabetes in women, but not men; (2) among women, the odds of being affected for carriers of PPARG A12 compared with noncarriers was 2.3 (95% CI; 1.4 - 3.8); and (3) among women, affected carriers of PPARG A12 had a significantly earlier age of onset and/or age at diagnosis compared with noncarriers. The authors concluded that, when taken together with the previously reported association of diabetes with HNF1A in both men and women, the



Oh et al. (2000) examined the relationship between the PPARG P12A mutation and obesity or diabetes in 229 Korean subjects. These included 111 obese subjects (body mass index, greater than 25 kg/m2). Of the subjects, 111 had normal glucose tolerance, 60 had impaired glucose tolerance, and 58 had diabetes mellitus. Allele frequencies of P12A were not different among Korean subjects with normal glucose tolerance, those with impaired glucose tolerance, and those with diabetes mellitus. Allele frequencies of PPARG A12 in obese subjects were not significantly different from those in nonobese subjects. The authors concluded that PPARG PA12 is not associated with either diabetes or obesity and may not be an important determinant of obesity or diabetes in Korean subjects.

Zhou et al. (2000) found this polymorphism in association with the H449H polymorphism (601487.0010) overrepresented in American patients with glioblastoma multiforme (137800). A similar association was not found in a German population.

Hasstedt et al. (2001) tested the hypothesis that the PPARG P12A variant is associated with the insulin resistance syndrome by genotyping 619 members of 52 familial type 2 diabetes kindreds. A subset of 124 family members underwent intravenous glucose tolerance tests and minimal model determination of insulin sensitivity. They estimated the frequency of the A12 allele as 0.12, within the range observed in random Caucasian samples. BMI, serum total cholesterol levels, triglyceride levels, systolic and diastolic blood pressures, and glucose concentration showed at least a trend to association when tested separately for a family-based association. When these 6 traits were included in a multivariate analysis, BMI, systolic and diastolic blood pressures, triglyceride levels, and glucose concentration remained significantly associated with the P12A variant, whereas the effect of P12A on liability for diabetes was not significant. The predicted means for each trait and each genotype suggested that the P12A variant acted most like a recessive mutation, with the major effect among homozygous individuals, who comprise only 1 to 2% of the population. The authors concluded that the results confirm an association of the P12A variant with traits commonly ascribed to the insulin resistance syndrome, but not with direct measure of insulin sensitivity. They stated that the tendency for this variant to act in a recessive manner with effects on multiple traits may explain the inconsistent associations noted in previous studies.

Polycystic ovary syndrome (PCOS, 184700) is common in women of reproductive age and is associated with a high risk for development of type 2 diabetes. Insulin resistance, a key component in the pathogenesis of PCOS and glucose intolerance, is ameliorated by the thiazolidinediones, synthetic ligands for PPARG. Hara et al. (2002) examined the relationship of the pro12-to-ala polymorphism in the PPARG gene to clinical and hormonal features of PCOS. Twenty-eight of 218 subjects had the ala allele, all in the heterozygous state. The frequency of the ala allele varied among the groups: 1% in African-Americans, 8% in Caucasians, and 15% in Hispanics. Nondiabetic Caucasians with an ala allele (pro/ala group) were more insulin sensitive than those in the pro/pro group, as evidenced by a lower homeostasis model assessment index and lower levels of insulin at both the fasting and 2 hour time points during the oral glucose tolerance test. The authors concluded that the pro12-to-ala polymorphism in the PPARG gene is a modifier of insulin resistance in Caucasian women with PCOS. 

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Population structure has been presumed to cause many of the disease-marker associations that have



been reported but not replicated, yet few actual case-control studies have been evaluated for the presence of structure. Ardlie et al. (2002) examined 4 case-control samples, comprising 3,472 individuals, to determine if detectable population subdivision was present. The 4 population samples included 500 U.S. whites and 236 African Americans with hypertension, and 500 U.S. whites and 500 Polish whites with type 2 diabetes, all with matched control subjects. Both diabetes populations were typed for the pro12-to-ala polymorphism of the PPARG gene, to replicate this well-supported association (Altshuler et al., 2000). In each of the 4 samples, Ardlie et al. (2002) tested for structure, using the sum of the case-control allele frequency chi-squared statistics for 9 short tandem repeat (STR) and 35 SNP markers (Pritchard and Rosenberg, 1999). They found weak evidence for population structure in the African American sample only. Further refinement of the sample to include only individuals with U.S.-born parents and grandparents eliminated the stratification. The example provided insight into the factors affecting the replication of association studies and suggested that carefully matched, moderate-sized case-control samples in cosmopolitan U.S. and European populations are unlikely to contain levels of structure that would result in significantly inflated numbers of false-positive associations. They also explored the role that extreme differences in power among studies, due to sample size and risk-allele frequency differences, may play in the replication problem.

## .0003 CANCER OF COLON [PPARG, 1-BP DEL, 472A]

In a sporadic colon cancer (114500) tumor, <u>Sarraf et al. (1999)</u> identified a somatic mutation in the PPARG gene, a 1-bp deletion at nucleotide 472, which resulted in a frameshift.

## .0004 CANCER OF COLON, SOMATIC [PPARG, GLN286PRO]

In a sporadic colon cancer (114500) tumor, <u>Sarraf et al. (1999)</u> identified a somatic mutation in the PPARG gene, an A-to-G transition at nucleotide 857, which resulted in a gln286-to-pro substitution.

## .0005 CANCER OF COLON, SOMATIC [PPARG, LYS319TER]

In a sporadic colon cancer (114500), <u>Sarraf et al. (1999)</u> identified a somatic mutation in the PPARG gene, an A-to-T transversion at nucleotide 955, which resulted in a lys319-to-ter substitution.

## .0006 CANCER OF COLON, SOMATIC [PPARG, ARG288HIS]

In a sporadic colon cancer (114500) tumor, <u>Sarraf et al. (1999)</u> identified a somatic mutation in the PPARG gene, a G-to-A transition at nucleotide 863, which resulted in an arg288-to-his substitution.

## .0007 DIABETES MELLITUS, INSULIN-RESISTANT, WITH ACANTHOSIS NIGRICANS AND HYPERTENSION [PPARG, PRO467LEU ]

In a patient with severe insulin resistance, type 2 diabetes mellitus, and hypertension (604367) who had been diagnosed in her twenties, Barroso et al. (1999) detected a C-to-T transition in the PPARG gene resulting in a proline-to-leucine mutation at codon 467 (P467L). Her son, aged 30 years, who also had a history of early-onset diabetes and hypertension, was also heterozygous for the P467L mutation. All other family members, including both parents of the proband, none of whom were known to have diabetes or hypertension, were homozygous for wildtype receptor sequence. Nonpaternity was excluded, indicating a de novo appearance of the mutation in the proband. §





# .0008 DIABETES MELLITUS, INSULIN-RESISTANT, WITH ACANTHOSIS NIGRICANS AND HYPERTENSION [PPARG, VAL290MET ]

In a 15-year-old patient with primary amenorrhea, hirsutism, acanthosis nigricans, elevated blood pressure, and markedly elevated fasting and postprandial insulin levels (604367), Barroso et al. (1999) identified a G-to-A transition in the PPARG gene resulting in a valine-to-methionine mutation at codon 290 (V290M). By age 17 the patient had developed type 2 diabetes and had hypertension which required treatment with beta-blockers. Her clinically unaffected mother and sister were both wildtype at this locus; screening of the deceased father was not possible.

## .0009 PPARG POLYMORPHISM C/T [PPARG, 161C-T]

Meirhaeghe et al. (1998) reported a 161C-T substitution in exon 6 of the PPARG gene. Since PPAR-gamma is a transcription factor implicated in adipocyte differentiation and in lipid and glucose metabolism, they analyzed the relationships between this genetic polymorphism and various markers of the obesity phenotype in a representative sample of 820 men and women living in northern France. The frequencies of the C and T alleles were 0.860 and 0.140, respectively. In the whole sample, no association of the polymorphism with the markers tested was observed, but a statistically significant interaction (P less than 0.03) existed between this polymorphism and body mass index (BMI) for plasma leptin levels. Obese subjects bearing at least one T allele had higher plasma leptin levels observed in women. Thus, for a given leptin level, the BMI was relatively lower in obese subjects carrying at least one T allele than in obese CC homozygotes. 

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Wang et al. (1999) studied this polymorphism in 647 Australian Caucasian patients aged 65 years or less, with or without angiographically documented coronary artery disease. The frequencies of the CC, CT, and TT genotypes were 69.8%, 27.7%, and 2.5%, respectively, and the T allele frequency 0.163. These frequencies were in Hardy-Weinberg equilibrium and not different between men and women. Wang et al. (1999) found that the T allele carriers (CT and TT genotypes) had significantly reduced coronary artery disease risk compared to the CC homozygotes, with an odds ratio of 0.457. Association with obesity (601665) was not found in these patients. The authors interpreted this to indicate that the PPARG gene may have a significant role in atherogenesis, independent of obesity and of lipid abnormalities, possibly via a direct local vascular wall effect.

## .0010 GLIOBLASTOMA, SUSCEPTIBILITY TO [PPARG, HIS449HIS]

Zhou et al. (2000) reported an overrepresentation of this polymorphism, a C-to-T transversion at nucleotide 1347, in American patients with glioblastoma (137800). This polymorphism was found in association with P12A (601487.0002) in these patients, but not in German patients with glioblastoma.

#### .0011 INSULIN RESISTANCE [PPARG, 3-BP DEL/1-BP INS, NT553]

In a Europid family in which 5 members in 2 generations had severe insulin resistance, <u>Savage et al.</u> (2002) found double heterozygosity for frameshift mutations in the PPARG gene and the PPP1RG3A gene (600917.0003).

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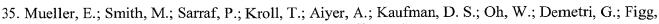
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Patricia A. Hartz - updated: 1/6/2003 John A. Phillips, III - updated: 12/30/2002 Victor A. McKusick - updated: 11/22/2002 Victor A. McKusick - updated: 10/21/2002 Victor A. McKusick - updated: 8/29/2002 Victor A. McKusick - updated: 8/16/2002 John A. Phillips, III - updated: 7/29/2002 John A. Phillips, III - updated: 7/25/2002 Victor A. McKusick - updated: 7/17/2002 Paul J. Converse - updated: 5/30/2002 Ada Hamosh - updated: 5/28/2002 Paul J. Converse - updated: 4/18/2002 John A. Phillips, III - updated: 2/20/2002 Dawn Watkins-Chow - updated: 2/1/2002 Stylianos E. Antonarakis - updated: 11/12/2001

Victor A. McKusick - updated: 9/5/2001 John A. Phillips, III - updated: 7/30/2001 Michael J. Wright - updated: 7/23/2001 John A. Phillips, III - updated: 7/2/2001 John A. Phillips, III - updated: 2/12/2001 John A. Phillips, III - updated: 2/9/2001 Stylianos E. Antonarakis - updated: 2/1/2001 Victor A. McKusick - updated: 10/26/2000

Ada Hamosh - updated : 9/1/2000

Victor A. McKusick - updated: 8/28/2000 Stylianos E. Antonarakis - updated: 6/9/2000

Paul J. Converse - updated: 6/7/2000 Ada Hamosh - updated: 5/24/2000 Paul J. Converse - updated: 5/16/2000 John A. Phillips, III - updated: 3/31/2000 Victor A. McKusick - updated: 2/18/2000

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Stylianos E. Antonarakis - updated: 11/19/1999 Stylianos E. Antonarakis - updated: 11/10/1999 Stylianos E. Antonarakis - updated: 7/20/1999 Victor A. McKusick - updated: 4/6/1999 Victor A. McKusick - updated: 10/22/1998 Stylianos E. Antonarakis - updated: 10/8/1998 Victor A. McKusick - updated: 10/2/1998 Stylianos E. Antonarakis - updated: 5/15/1998 Victor A. McKusick - updated: 4/23/1998

## CREATION DATE

1

Jennifer P. Macke: 11/4/1996

## **EDIT HISTORY**

mgross: 1/6/2003 mgross: 1/6/2003 alopez: 12/30/2002 cwells: 11/22/2002 terry: 11/20/2002 alopez: 11/4/2002 alopez: 10/30/2002 terry: 10/21/2002 mgross: 9/19/2002 tkritzer: 9/4/2002 terry: 8/29/2002 tkritzer: 8/23/2002 tkritzer: 8/21/2002 terry: 8/16/2002 alopez: 8/6/2002 terry: 8/2/2002 tkritzer: 7/29/2002 tkritzer: 7/29/2002 tkritzer: 7/29/2002 tkritzer: 7/25/2002 tkritzer: 7/25/2002

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carol: 10/26/1998

dholmes: 5/15/1998 carol: 4/23/1998 terry: 4/14/1998 dholmes: 1/26/1998 carol: 11/4/1996

# ALLELIC VARIANTS (selected examples)

• 0001: OBESITY, SEVERE

Mutation: PPARG, PRO115GLN





- 0002 : DIABETES MELLITUS, TYPE II, RESISTANCE TO
  - Mutation: PPARG, PRO12ALA
- 0003 : CANCER OF COLON
  - Mutation: PPARG, 1-BP DEL, 472A
- 0004 : CANCER OF COLON, SOMATIC
  - Mutation: PPARG, GLN286PRO
- 0005 : CANCER OF COLON, SOMATIC
  - Mutation: PPARG, LYS319TER
- 0006 : CANCER OF COLON, SOMATIC
  - Mutation: PPARG, ARG288HIS
- <u>0007 : DIABETES MELLITUS, INSULIN-RESISTANT, WITH ACANTHOSIS NIGRICANS AND HYPERTENSION</u>
  - Mutation: PPARG, PRO467LEU
- <u>0008</u>: <u>DIABETES MELLITUS, INSULIN-RESISTANT, WITH ACANTHOSIS NIGRICANS</u> AND HYPERTENSION
  - Mutation: PPARG, VAL290MET
- 0009: PPARG POLYMORPHISM C/T
  - Mutation: PPARG, 161C-T
- 0010: GLIOBLASTOMA, SUSCEPTIBILITY TO
  - Mutation: PPARG, HIS449HIS
- 0011: INSULIN RESISTANCE
  - Mutation: PPARG, 3-BP DEL/1-BP INS, NT553